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### **REMARKS**

Claims 1-16 and 18-74 are currently pending. Claims 67-69 stand withdrawn from consideration as being directed to a non-elected invention. Applicants reserve the right to pursue these claims in a later filed application claiming the benefit of the subject application. Claims 1-16, 18-66 and 70-74 are under examination. Claims 1, 34 and 71 have been amended. Support for the amendment can be found throughout the application as filed, including for example, at paragraphs 0025 and 0112 and in the Examples. Accordingly, these amendments do not raise an issue of new matter, and entry thereof is respectfully requested.

Applicants will submit a Supplemental Information Disclosure Statement with copies of the omitted references referred to at page 3 of the Office Action.

### **Rejections Under 35 U.S.C. § 103**

Claims 1-12, 14, 15, 18-28, 30, 32-46, 48-49, 51-63 and 70-74 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Hatzimanikatis et al., *AICHE Journal* 42:1277-1292 (1996), in view of Varma et al., *Bio/Technology* 12:994-998 (1994) and further in view of Grewal et al., *Protein Engineering* 7:205-211 (1994). Applicants respectfully traverse and will address each point of the Examiner's response in turn below.

Reason 1 (Office Action at p.16): The Examiner alleges that Applicants argue at page 15 of the Response filed May 21, 2010, that there is no reasonable expectation of success if Hatzimanikatis et al. and Varma et al. are combined.

Applicants respectfully point out that page 15 merely sets up the basis for the factual analysis that follows on pages 16-20. The basis being that obviousness requires a comparison of all limitations with the prior art (*In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995)); a suggestion of all limitations in a claim (*CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003)), and that there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness (*KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007)). The last paragraph at page 15 of Applicants' Response summarizes the above legal

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standard and the claims in issue. If there is an argument being made at page 15 other than the basis for rebuttal Applicants would appreciate being informed so the Examiners' comments can be adequately addressed.

With respect to Applicants' argument regarding lack of any suggestion, motivation or expectation of success, Applicants respectfully draw the Examiner's attention to page 19, para. 3 through page 20, line 4 of Applicants' previous Response.

Reason 2 (Office Action at p.16): The Examiner alleges that the studies of Hatzimanikatis et al. and Varma et al. both pertain analogously to understanding the mechanisms behind molecular synthesis and metabolism. This statement appears to ignore Applicants remarks at pages 16-20 and Exhibit A submitted therewith. Applicants set forth at pages 16-20 of the Response filed May 21, 2010, that the approaches of Hatzimanikatis et al. and Varma et al. are distinct and non-analogous. As summarized, in part, therein:

First, each model utilizes a different computational approach to model cellular networks [and] [s]econd, . . . one skilled in the art would not have been motivated to combine a non-analogous stoichiometric method that can be less desirable with an [*sic*] method already well suited for studying changes in regulatory structures because it would impart unnecessary limitations without . . . adding any advantages.

Response filed May 21, 2010, at p. 19, para. 1-2.

Applicants reassert the supporting arguments at pages 16-20, including Exhibit A, for the above conclusion and respectfully request reconsideration of the Examiner's rationale that non-analogous computational methods are analogous because they are both directed to studies of molecular synthesis and metabolism (see also, page 19, para. 3 through page 20, line 4).

Reason 3 (Office Action at p.16): The Examiner appears to allege in support of the above position of Reason 2 that Hatzimanikatis et al. implicitly teaches an elementary version of a stoichiometric matrix. The purported rationale is that the pathway illustrated in Figure 1 at page 1283 constitutes a "binary" stoichiometric matrix where the stoichiometric coefficient is

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either unity when the biomolecule is part of the aromatic amino acid synthesis pathway and zero if it is not. *Id.* (quotes original).

Applicants fail to comprehend or appreciate the above analogy. As claimed, a stoichiometric matrix relates a plurality of reactions of a biochemical reaction wherein each reaction includes a substrate, a product and a stoichiometric coefficient relating the substrate and product, and wherein at least one of said reactions is a regulated reaction. A “stoichiometric coefficient” is described in the application as:

[A] numerical constant correlating the quantity of one or more reactants and one or more products in a chemical reaction . . . each with a discrete stoichiometric coefficient assigned to them to describe the chemical conversion taking place in the reaction.

*Id.* at paragraph 0041 (emphasis added).

Arbitrarily assigning a biomolecule in Figure 1 of Hatzimanikatis et al. a stoichiometric coefficient of either unity or zero due to its presence or absence in the pathway does not relate a plurality of reactions where the stoichiometric coefficient correlates the quantity of one or more reactants and one or more products in a chemical reaction that describes the chemical conversion taking place in the reaction. Rather, such an arbitrary assignment at most provides the presence or absence of that particular biomolecule.

Reason 4 (Office Action at p.17): Applicants remarks on page 16 of the Response filed May 21, 2010, regarding the amendment directed to determining a systemic property that is predictive of a biochemical reaction network of an organism is alleged to be unpersuasive. Applicants respectfully point out and restate for the record that the amendment distinguishes the hypothetical regulatory superstructure described in Hatzimanikatis et al. Further, Figure 1 in Hatzimanikatis et al, relied on the Examiner does not appear to show a flux distribution as alleged. Rather, Figure 1 merely shows an amino acid synthesis pathway.

Reason 5 (Office Action at p.17-18): Referencing equation 1 in Varma et al. and Figure 1 in Hatzimanikatis et al., the Examiner alleges that the embodiments relied on in these

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publications pertain to stoichiometric models and concludes that Applicants' argument that the computational approaches are non-analogous is not persuasive.

As set forth above, Applicants fail to comprehend or appreciate the analogy that Figure 1 of Hatzimanikatis et al. corresponds to a "binary stoichiometric matrix." Arbitrarily assigning a biomolecule a stoichiometric coefficient of either unity or zero due to its presence or absence does not relate a plurality of reactions where the stoichiometric coefficient correlates the quantity of a reactant and a product that describes the chemical conversion taking place.

Further, Applicants provided extrinsic evidence showing that the computational approaches of Hatzimanikatis et al. and Varma et al. are distinct and non-analogous such that one skilled in the art would not have arrived at the claimed invention based on the teachings in the references or based on the teachings in the references together with knowledge generally available in the art (see Response filed May 21, 2010, at page 16, para. 4 through page 20, para. 1).

Reason 6 (Office Action at p.18): The Examiner further alleges that the claims lack an element that would exclude kinetic models such that the references would not be combinable.

Applicants respectfully disagree. The claims explicitly recite solving a mathematical optimization problem using the claimed stoichiometric matrix by determining at least one flux distribution that minimizes or maximizes an objective function when said constraint set is applied to said data structure. This recitation of elements is believed to distinguish kinetic models such as those described in Hatzimanikatis et al. (see, for example, Application at para. 0167 where the claimed model is compared to a kinetic model) and such distinction is supported by Exhibit A of the response filed May 21, 2010 (see, for example, Response at page 17, para. 3 through page 18, para. 3). To more explicitly state the distinction between kinetic and stoichiometric-based models, Applicants have amended the claims to recite Flux Balance Analysis (FBA) is employed to solve the optimization problem that utilizes the claimed stoichiometric matrix. Accordingly the computational approaches of Hatzimanikatis et al. and Varma et al. are non-analogous such that one skilled in the art would not have arrived at the

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claimed invention based on the teachings in the references alone or together with knowledge generally available in the art.

Reason 7 (Office Action at p.18): The Examiner further alleges that Applicants' have not provided any evidence or reasoning as to why the extra limitations of Hatzimanikatis et al. are undesirable or unnecessary and that the open language of the claims includes such undesirable or unnecessary limitations.

Applicants respectfully disagree. Preliminarily, Applicants fail to understand why the open claim language is relevant to this point because Applicants remarks were directed to why one skilled in the art would not have arrived at the claimed invention based on the combination of cited art.

Applicants draw the Examiner's attention to Exhibit A and Applicants' remarks thereto at page 17, para. 3 through page 19, para. 2, of the Response filed May 21, 2010. Exhibit A and Applicants' remarks thereto provide sufficient evidence and reasoning why one skilled in the art would not have had an incentive to combine Hatzimanikatis et al. with Varma et al. In this regard, the quoted passage from Exhibit A specifically points out that "in the absence of detailed kinetic and thermodynamic data . . . [the versatility of flux balance analysis] comes at the expense of perhaps unknowingly crossing kinetic or regulatory flux barriers." (Response at page 18, top (emphasis Applicants)). Based on the teachings of Exhibit A, Applicant concluded:

As pointed out in both Varma et al. and in Exhibit A, stoichiometry-based models are an alternative model to kinetic-based models. Further, Exhibit A describes that kinetic models are well suited for exploring enzyme activities and regulatory structures. In contrast, stoichiometric models do not utilize kinetic information and can be less desirable than kinetic models because they can unknowingly cross flux barriers.

Response at page 18, para. 3.

Thus, as stated at page 19, para. 2, of Applicants' previous Response, because the two computational approaches are non-analogous and suited for different purposes, one skilled in the

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art would not have been motivated to combine a method that can be less desirable with a method already well suited for studying changes in regulatory structures.

Reason 8 (Office Action at p.18): The Examiner further alleges that the pathways of Hatzimanikatis et al. illustrate a quantitative stoichiometric matrix apparently because of the arbitrary binary assignment of unity and zero for the presence or absence of a biomolecule and, thus, it is combinable with the stoichiometric matrices of Varma et al.

Applicants previous set forth above why Figure 1 of Hatzimanikatis et al. should not be analogized to a stoichiometric matrix of Varma et al. Such remarks are equally applicable in response to the Examiner's reasoning here. Accordingly, absent additional information that substantiates such an analogy, Applicants maintain that the cited combination fails to render the invention as claimed obvious.

In light of the above remarks, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Claims 31 and 64-66 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Hatzimanikatis et al., *supra*, in view of Varma et al., *supra*, and Grewal et al., *supra*, and further in view of Liao et al., *Biotechnol. Bioengineer.* 52:129-140 (1996). Applicants respectfully traverse. This rejection relies on Hatzimanikatis et al. in view of Varma et al. and, as discussed above, Applicants have set forth the deficiencies of Hatzimanikatis et al. in view of Varma et al. and Grewal et al. and Liao et al. does not cure these deficiencies. Accordingly, the claimed methods are unobvious over the cited combination of references and withdrawal of this ground of rejection is respectfully requested.

Claims 16 and 50 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious over Hatzimanikatis et al., *supra*, in view of Varma et al., *supra*, and Grewal et al., and further in view of Kim et al., U.S. publication 2002/00087275. Applicants respectfully traverse. This rejection relies on Hatzimanikatis et al. in view of Varma et al., and Applicants have set forth above the deficiencies in the combination of these primary and secondary references. Kim et al. does not

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cure these deficiencies alone or in combination with Grewal et al. Accordingly, the claimed method is unobvious over the cited combination of references and withdrawal of these ground of rejection is respectfully requested.

Claims 13 and 47 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Hatzimanikatis et al., *supra*, in view of Varma et al., *supra*, and Grewal et al., *supra*, and further in view of Vissing et al., *Neurology* 47:766-771 (1996). Applicants respectfully traverse. This rejection relies on Hatzimanikatis et al. in view of Varma et al., and Applicants have set forth above the deficiencies in the combination of these primary and secondary references Vissing et al. does not cure these deficiencies alone or in combination with Grewal et al. Accordingly, the claimed computer readable medium or media and method are unobvious over the cited combination of references and withdrawal of this ground of rejection is respectfully requested.

Claim 29 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious over Hatzimanikatis et al., *supra*, in view of Varma et al., *supra*, and Grewal et al., *supra*, and further in view of Callis, *Plant Cell* 7:845-857 (1995). Applicants respectfully traverse. As discussed above, Applicants have set forth the deficiencies of Hatzimanikatis et al. in view of Varma et al. and/or Grewal et al. Moreover, Applicants respectfully submit that Callis does not cure the deficiencies of this combination of references. As set forth previously of record, Callis is a review article discussing regulation of protein degradation in plants. Furthermore, Applicants respectfully submit that the passage on page 850 of Callis referred to in the Office Action describes the senescent process in unpollinated pea ovaries and the induction of a cysteine protease during this process. There is no teaching or suggestion of annotation of at least one reactant in a plurality of reactants or at least one reaction in a plurality of reactions by assignment to an open reading frame, as in Applicants' claim. Applicants respectfully maintain that Callis provides no motivation as asserted in the Office Action. Therefore, Applicants respectfully submit that Callis does not cure the deficiencies of Hatzimanikatis et al. in view of Varma et al. and/or Grewal et al. Accordingly, the claimed computer readable medium or media is unobvious over the cited combination of references and withdrawal of this ground of rejection is respectfully requested.

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**CONCLUSION**

In light of the amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully requests a notice to this effect. Should the Examiner have any questions, the Examiner is invited to call the undersigned attorney.

The Commissioner is hereby authorized to charge \$555.00 as payment for the Petition for a three-Month Extension of Time fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

  
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